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Brief report

# Treatment adherence with vildagliptin compared to sulphonylurea as add-on to metformin in Muslim patients with type 2 diabetes mellitus fasting during Ramadan

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## Abstract

**Objective:**
To assess treatment adherence to dipeptidyl peptidase-4 inhibitor vildagliptin compared with sulphonylureas (SU) in Muslim patients with type 2 diabetes mellitus who were fasting during Ramadan in the UK.

**Research design and methods:**
This prospective, observational cohort study was conducted in four UK centres. Patients already taking vildagliptin (50 mg twice a day) or an SU as add-on therapy to metformin were followed up for ≤16 weeks. They were asked to record all missed doses of anti-diabetes medications.

**Results:**
Of the 72 patients enrolled (vildagliptin, $n=30$; SU, $n=41$; not allocated to treatment, $n=1$), 59 (81.9%) completed the study (vildagliptin, $n=23$; SU, $n=36$), including one patient in the SU arm who completed but failed to provide information on missed doses; all patients in the SU arm were taking gliclazide. In the vildagliptin arm one patient (4.3%) missed a total of four doses while in the SU arm 10 patients (27.8%) missed a total of 266 doses (mean [SD] number of doses missed per patient: 26.6 [16.5]). The mean (SD) proportions of doses missed during fasting were 0.2% (0.9) and 10.4% (21.7) in the vildagliptin and SU arms, respectively, with a significant mean between-group difference of −10.2% (95% CI: −19.3%, −1.1%; $p=0.0292$). There were no patients in the vildagliptin arm who missed more than 20% of OAD doses compared with 19.4% in the SU arm ($p=0.0358$). Of the patients receiving an SU, 15 (42%) collectively reported 34 hypoglycaemic events (HEs) and one grade 2 HE; of these, fewer were non-adherent ($n=6$, 40%) than adherent ($n=9$, 60%). No patients reported HEs in the vildagliptin arm.

**Conclusion:**
During Ramadan fasting, treatment with vildagliptin resulted in better treatment adherence compared with SU in Muslim patients with type 2 diabetes mellitus. Study limitations are the sample size and the lack of diet and exercise data.

## Introduction

Fasting in patients with type 2 diabetes mellitus (T2DM) can be associated with increased risk of both hypoglycaemia and hyperglycaemia. When using drugs known to be associated with hypoglycaemia this risk is potentially higher and glycaemic control deteriorates in some patients with diabetes who fast during Ramadan[1].

In patients with T2DM, fasting increases the risk of severe hypoglycaemia by 7.5 times and hospitalisation due to hypoglycaemia by five times[2]. Hypoglycaemia is an important limiting factor in managing glycaemic control in patients with T2DM and is also a significant barrier to treatment adherence[3]. Apart from increased risk of hypoglycaemia and hyperglycaemia, another challenge during Ramadan fasting is compliance with treatment. Studies have shown that patients change the intake of drug doses and time without seeking appropriate health care professional advice[4]. Furthermore, adherence to prescribed oral anti-diabetes drugs (OADs) is poor in South Asian patients[5]. Although a number of factors are attributable to poor treatment compliance during Ramadan, one of the factors emerging is episodes of unreported hypoglycaemia that could be responsible for patients omitting their drugs in order to avoid the unpleasant side-effects of hypoglycaemia and continue their fasting.

It has also been shown that patients may consider altering and adjusting the drug dose and timing appropriately in order to avoid hypoglycaemia and enable completion of fasting during Ramadan[6]. Considering the potential medical complications and poor treatment adherence associated with fasting, the choice of OAD therapy is therefore particularly important.

Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor that improves glycaemic control by increasing $\alpha$- and $\beta$-cell responsiveness to glucose. It significantly reduces the risk of hypoglycaemia versus sulphonylureas (SUs)[7,8].

Results from the VECTOR (Vildagliptin Experience Compared To gliclazide Observed during Ramadan) study showed that, in Muslim patients with T2DM fasting during Ramadan, vildagliptin as add-on to metformin reduced glycated haemoglobin levels (HbA1c) without hypoglycaemia in contrast to gliclazide add-on to metformin[9]. The present report highlights the missed doses and treatment adherence during Ramadan fasting from the previously published VECTOR study.

# Methods

## Study design and patients

This was a post-authorisation, prospective, observational, non-interventional study conducted at four centres in the UK ($N = 72$). Patients were enrolled into two cohorts: vildagliptin (50 mg b.i.d.) plus metformin or SU plus metformin. Data were collected over a period of $\leq$16 weeks at two data collection points, occurring 1–6 weeks prior to commencement of fasting and $\leq$6 weeks after the fasting period ended. Patients aged $\geq$18 years and diagnosed with T2DM $\geq$12 months prior to fasting were enrolled, provided they had received vildagliptin or SU add-on to metformin for $\geq$4 weeks prior to fasting, were planning to fast for $\geq$10 days and had HbA1c $\leq$8.5% up to 1 month prior to fasting. Further details of the study design and patient exclusion criteria are reported by Hassanein *et al.*[9].

## Efficacy assessments

The main efficacy assessment was adherence to treatment during Ramadan fasting. Treatment adherence was assessed by expressing the number of doses missed (as recorded in a patient-held diary) as a percentage of the total number of doses prescribed. Subjects were also categorised into whether they missed >20% of doses or not.

## Safety and tolerability

All adverse events (AEs) and serious AEs (SAEs) were recorded and treated appropriately at the clinicians' discretion. The suspected involvement of anti-diabetes medication in any SAE, including grade 2 HEs (and any recurrence), was also recorded. Routine liver function tests were performed.

## Statistical analysis

The difference in percentage doses missed (vildagliptin minus SU) was tested by an unpaired *t*-test together with a 95% confidence interval (CI) for the treatment difference. The proportion of patients missing or not missing >20% of OAD doses in each group was tested with Fisher's exact test.

## Ethics

This observational study was conducted in accordance with applicable local regulations and the ethical principles of the Declaration of Helsinki (and any subsequent amendments). Patients provided written informed consent before any assessment was performed. The study protocol and informed consent forms were reviewed and approved by the Multi-centre Research Ethics Committee for Wales.

# Results

Of the 72 patients enrolled, 59 (81.9%) completed the study (vildagliptin, $n = 23$ [76.7%]; SU, $n = 36$ [87.8%]) including one patient in the SU arm who completed but failed to provide information on missed doses. Patient demographics and baseline characteristics are presented in Table 1. Mean ages were comparable between groups and most patients were aged <65 years. There were more



 

Table 1. Patient demographics and baseline characteristics.

| Demographic/baseline variable | Vildagliptin cohort $n=23$ | Sulphonylurea cohort $n=36$ | $p$-value# |
|---|---|---|---|
| Age (years) | 58.3 ± 13.06 | 57.3 ± 11.03 | 0.6135 |
| <65 years, *n* (%) | 17 (73.9) | 28 (77.8) | 0.7618 |
| ≥65 years, *n* (%) | 6 (26.1) | 8 (22.2) | |
| Sex, *n* (%) | | | |
| Male | 12 (52.2) | 21 (58.3) | 0.7889 |
| Female | 11 (47.8) | 15 (41.7) | |
| Ethnicity, *n* (%) | | | |
| South Asian | 23 (100) | 34 (94.4) | 0.5161 |
| Other | 0 | 2 (5.6) | |
| BMI (kg/m$^2$) | 29.6 ± 5.0 | 28.5 ± 3.9 | 0.3632 |
| T2DM duration (years) | 7.1 ± 6.1 | 5.8 ± 4.7 | 0.4553 |
| $HbA_{1c}$ (%) | 7.7 ± 0.9 | 7.2 ± 0.6 | – |
| Any dose adjustments for Ramadan, *n* (%) | 0 | 5 (13.9) | – |
| Metformin adjusted | 0 | 4 (11.1) | – |
| Vildagliptin adjusted | 0 | – | – |
| Gliclazide adjusted | – | 3 (8.3) | – |
| Median total dose before fasting, mg/day | | | |
| Metformin | 2000 | 2000 | – |
| Vildagliptin | 100 | – | – |
| Gliclazide | – | 80* | – |
| Median total dose after Ramadan adjustments, mg/day | | | |
| Metformin | 2000 | 2000 | – |
| Vildagliptin | 100 | – | – |
| Gliclazide | – | 80* | – |

Data are shown mean ± SD, unless otherwise stated.
#*p*-value Wilcoxon two-sample test for continuous variables, Fisher's exact test for categorical variables.
*Different formulations were used for gliclazide therefore the following conversion factor was used: 80 mg standard formulation ≡ 30 mg modified release formulation.

men ($n=33$, 55.9%) than women ($n=26$, 44.1%) and nearly all patients were South Asians. Patients in the vildagliptin group had longer T2DM duration than the SU group and a slightly higher BMI and HbA1c. Mean duration of fasting in both arms were comparable (vildagliptin 25.0 ± 6.6 days vs. SUs 25.4 ± 5.8 days). Discontinuations were due to loss to follow-up and included patients who chose not to fast, did not attend the second visit or did not take any medication. All patients who completed the study were eligible for inclusion in the per protocol and safety populations.

## Efficacy outcomes

In the vildagliptin arm, one patient (4.3%) missed a total of four doses; in the SU arm, 10 patients (27.8%) missed a total of 266 doses (mean [SD] number of doses missed per patient: 26.6 [16.5]). The mean (SD) proportion of doses missed during fasting was 0.2% (0.9%) in the vildagliptin arm and 10.4% (21.7%) in the SU arm, with a significant between-group difference of −10.2% (95% CI: −19.3%, −1.1%); $p=0.0292$. There were no patients in the vildagliptin arm who missed more than 20% of OAD doses compared with 19.4% in the SU arm ($p=0.0358$) (Figure 1). Of the patients receiving an SU, 15 (42%) collectively reported 34 HEs and one grade 2 HE; of these patients, fewer were non-adherent ($n=6$, 40%) than adherent ($n=9$, 60%). Further details of the study results are reported by Hassanein *et al.*[9]

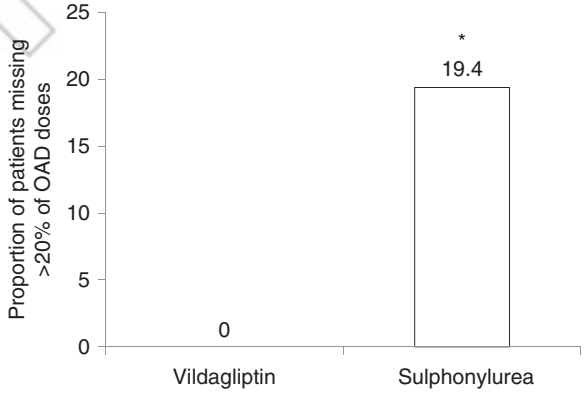


Figure 1. Proportion of patients missing >20% of drug doses during Ramadan fasting. *$p=0.0358$ vs. SU.

## Discussion

In this real-world observational study of Muslim patients with T2DM fasting during Ramadan, a marked difference in missed doses between the vildagliptin and SU treatment groups was observed with only one patient (4.3%) in the vildagliptin group missing at least one dose compared with

10 patients (27.8%) in the SU group. This equates to four missed doses in the vildagliptin arm compared with 266 in the SU arm. Better treatment adherence with vildagliptin was most likely due to better tolerability with patients having less fear of hypoglycaemia, which is a significant barrier to adherence and can adversely affect quality of life by causing distress and serious morbidity[3]. Furthermore, better adherence was found to be associated with improved glycaemic control in the vildagliptin arm[9].

Patients' self-management and adherence to drugs are key to good glycaemic control. Several studies have shown that patients arbitrarily change the intake of drug doses and time without seeking medical advice[5]. It has also been noted that adherence to prescribed OADs in certain patient populations, such as South Asian patients, is poor, that they give less importance to controlling their diabetes, and they may be less anxious than white patients about adhering to their treatments[4]. For example, Pakistani and Indian patients may adjust their OADs according to symptoms. It is increasingly recognised that if adherence is to be improved, patients' perspectives must be better understood[4].

The results from the present study show that with vildagliptin there were no HEs reported as compared with nearly half of the patients in the SU group experiencing HEs. The difference in the proportion of patients experiencing HEs in the present study (−41.7%) was in line with previous findings in favour of vildagliptin from a UK retrospective audit in T2DM patients fasting during Ramadan (−53.8%)[10]. Furthermore, results from a recent observational study that compared sitagliptin with SU treatment also showed a low risk of hypoglycaemia with sitagliptin compared with the SU arm in patients with T2DM fasting during Ramadan[11]. Improvement in HbA1c was found to be significant with vildagliptin than SU despite the short study duration[9]. This may be due to better adherence, less defensive eating, and/or higher baseline HbA1c in patients in this cohort (7.7% vs. 7.2%) than the SU group. This study had some limitations, including the small sample size and a lack of diet, eating pattern, and exercise data.

As Muslim patients with T2DM may still choose to fast during Ramadan, it is important that fasting is made as safe as possible in this patient population. Use of DPP-4 inhibitors in fasting patients has been shown to improve glucose control with low risk of hypoglycaemia as well as better treatment adherence[9]. For physicians, this translates to less time and fewer resources spent treating complications of hypoglycaemia and uncontrolled blood glucose, a safer option for achieving glycaemic targets, and, ultimately, a reduction in cost.

Our findings are an important addition to the existing evidence that helps physicians choose between classes of OAD therapy. If our study is representative of the 260,000 UK Muslims with T2DM believed to fast during Ramadan each year, many of whom would be on a similar therapeutic combination, this will have significant public health and clinical implications.

## Conclusion

In this study, during Ramadan fasting, almost all Muslim patients with T2DM receiving vildagliptin add-on to metformin adhered to treatment and none reported HEs. In contrast, nearly half the studied patients receiving an SU add-on to metformin experienced HEs and almost one-third missed doses. Of note, the majority of patients who experienced HEs were adherent to their therapy. Our findings highlight the importance of choosing an OAD therapy that matches the patient's lifestyle and suggest that vildagliptin is a suitable treatment option in Muslim patients with T2DM who fast during Ramadan.

## Transparency

**Declaration of funding**

This study was funded by Novartis Pharmaceuticals UK Ltd, who helped in the study design and in the collection, analysis and interpretation of data. The co-authors from Novartis were also involved in writing the manuscript and in the decisions during submission for publication.

**Declaration of financial/other relationships**

A.H.B. has received honoraria for lectures and advisory work from Novartis Pharmaceuticals Corporation, Merck Sharp & Dohme Limited, Bristol-Myers Squibb Company, AstraZeneca LP, Boehringer Ingelheim, Takeda, Eli Lilly and Company, Novo Nordisk A/S, and Sanofi-Aventis. W.H. has received research grants and honoraria from and acted as a consultant for Novartis Pharmaceuticals Corporation, Novo-Nordisk and Merck Sharp and Dohme. W.M. has received educational grant sponsorship to attend scientific meetings and honoraria for lectures from Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Eli Lilly and Company, AstraZeneca LP and Merck Sharp & Dohme Limited. M.H. has no conflict of interests with the study sponsors, but has received honoraria for lectures and Advisory Boards with Eli Lilly, and honoraria for lectures with Takeda, Novo Nordisk, Merck Sharp & Dohme Limited, Boehringer Ingelheim and Sanofi-Aventis. A.K. and M.A. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. P.G. and C.A. are employees of Novartis Pharmaceuticals UK Ltd, Frimley, UK, and C.A. owns shares in Novartis.

*CMRO* peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

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## References

1. Al-Arouj M, Boguerra R, Buse J, et al. Recommendations for management of diabetes during Ramadan. Diabetes Care 2005;28:2305-11
2. Salti I, Benard E, Detournay B, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care 2004;27:2306-11
3. Amiel SA, Dixon T, Mann R, et al. Hypoglycaemia in type 2 diabetes. Diabetes Med 2008;25:245-54
4. Aadil N, Houti IE, Moussamih S. Drug intake during Ramadan. BMJ 2004;329:778-82
5. Lawton J, Ahmad N, Hallowell N, et al. Perceptions and experiences of taking oral hypoglycaemic agents among people of Pakistani and Indian origin: qualitative study. BMJ 2005;330:1247
6. Ahmedani MY, Haque MS, Basit A, et al. Ramadan Prospective Diabetes Study: the role of drug dosage and timing alteration, active glucose monitoring and patient education. Diabet Med 2012;29:709-15
7. Ferrannini E, Fonseca V, Zinman B, et al. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metab 2009;11:157-66
8. Matthews DR, Dejager S, Ahren B, et al. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. Diabetes Obes Metab 2010;12:780-9
9. Hassanein M, Hanif W, Malik W, et al. Comparison of the dipeptidyl peptidase-4 inhibitor vildagliptin and the sulphonylurea gliclazide in combination with metformin, in Muslim patients with type 2 diabetes mellitus fasting during Ramadan: results of the VECTOR study. Curr Med Res Opin 2011;27:1367-74
10. Devendra D, Gohel B, Bravis V, et al. Vildagliptin therapy and hypoglycaemia in Muslim type 2 diabetes patients during Ramadan. Int J Clin Pract 2009;63:1446-50
11. Al Sifri S, Basiounny IA, Echtay A, et al. The incidence of hypoglycaemia in Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan: a randomised trial. Int J Clin Pract 2011;65:1132-40